BMT Tandem Meeting
Regulatory Issues Session

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Guidance for Industry

Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies

January 17, 2007

72 FR 1999

Draft Guidance

- For comment purposes only
- Comment period ends April 17, 2007
- Does not establish legally enforceable responsibilities
- Represents FDA's current thinking
- Recommendations, unless specific regulatory or statutory requirements cited
- Can use an alternative approach

Purpose

- Recommends ways for cord bank to apply for licensure for specified indications
- Explains applicable regulations in Title 21 of the Code of Federal Regulations
- Provides other information about the manufacture of HPC-C and how to comply with the applicable regulatory requirements

Scope

- Covers cord blood products that are:
  - Minimally manipulated; and
  - Intended for hematopoietic reconstitution in patients with hematological malignancies; and
  - Intended to be used in recipients unrelated to the donor
- Does not cover:
  - PBSC
  - Other cord blood products (e.g. more than minimally manipulated, and/or for other indications)
  - Cord blood for autologous/family-related use (though encourage following these recommendations)

Why is the indication limited?

- Cord blood regulated as HCT/P
- Homologous use broadly defined – hematopoietic reconstitution
- Preponderance of data submitted to docket describing cord blood transplant outcomes in patients with hematologic malignancies (approximately 65-70%)
- Numerous other indications – much less data (all genetic disease 25%, SAA/FA 5%)

Use of this Guidance

- Demonstrate that you have followed recommendations
- You may modify any procedure in guidance
  - Present evidence demonstrating that modification will provide assurances of safety, purity, potency, and effectiveness
- License would apply to HPC-C manufactured after approval, and to HPC-C previously manufactured in accordance with the information provided in the license where documentation provided to demonstrate comparability
- You may submit BLA containing your own data from clinical studies

Background

- History of promulgation of HCT/P regulations
- Summary of 1998 FR notice: Request for Proposed Standards
- Summary of 2003 BRMAC cord blood meeting
- Determination that data submitted to docket and published literature permit development of BLA recommendations

Applicable Regulatory Requirements

- Prelicense inspection
- 21 CFR Parts 210 and 211 (CGMP), 600 (Biological Products: General), 610 (Biological Products Standards), 201 and 610 Subpart G (labeling), 202 (advertising)
- 21 CFR 1271 HCT/P regulations
  - More specific regs supercede more general
  - Compliance with CGMP would result in compliance with applicable CGTP requirements, with some exceptions
- Use Section VII of Guidance as a reference

License Application Procedure

- Form FDA 356h – Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
- Where to submit – Document Control Center (address provided)
- What information to include
- What action FDA will take

Information to include

- Index
- Representative draft labeling
- Summary of information submitted
- CMC – 21 CFR 314.50(d); § 601.2
  - Full description of manufacturing process and SOPs for critical procedures, assays
- Summary validation data
- Establishment description – § 600.10
- Other attachments, including citation to data in docket

What action will FDA take?

- Review application
- Schedule prelicense inspection as soon as possible after receiving complete application
- If application not complete, identify/advise you of additional information that you will need to submit

Chemistry, Manufacturing and Controls (CMC) Section

- HPC-C Description and Characterization
- Manufacturers
- Methods of Manufacturing
- Container Closure System
- Environmental Assessment
- Methods Validation/Verification
- Labeling

Required and recommended test results

- Safety: ID testing, Sterility testing, Hb
- Purity and potency (pre-cryopreservation)
  - TNC ≥ 5.0 x 10^8/HPC-C
    - Based on 20 kg recipient dose of ≥ 2.5 x 10^7/kg and 70% post-thaw recovery = 1.7 x 10^7/kg
  - Viable nucleated cells ≥ 85%
  - Viable CD34+ cells ≥ 1.25 x 10^6/HPC-C
    - Based on CD34+ cells ≥ 0.25% prior to freezing
- Identity: HLA typing, confirmatory typing using attached segment, ABO/Rh

Manufacturer information

- Identification
  - Includes FDA registration number, contract manufacturers (collection sites, labs performing RCDAD and product sterility testing)
- Floor diagrams
  - Not necessary for collection sites
- Contamination precautions

Methods of manufacturing

- SOPs to submit
  - Collection, processing, selection, shipping and handling (including thawing and preparation for administration, salvage
- Validation data summary
  - Recommend data from 3 consecutive, separate HPC-Cs

HPC-C manufactured using different procedures

- Separate validation summary including data demonstrating:
  - Comparability between the previously manufactured HPC-C and those manufactured currently
    - Product characteristics
    - Clinical outcome data
    - References on comparability in Guidance
  - Evidence that methods, facilities, and controls used for manufacture conform to CGMP and other applicable regulatory requirements

Other CMC information

- Description of container closure system
  - Can reference NDA, 510(k), or MF
  - Provide evidence of container and closure integrity for duration of proposed storage period
- Environmental assessment – 21 CFR Part 25
  - May submit request for categorical exclusion
- Methods validation/verification
  - Infectious disease tests – licensed/approved/cleared
  - Other tests – sterility, TNC, HLA, ABO/Rh, other
- Labeling – see guidance Section VII.B.2

Establishment Description

- General Information
  - Floor diagram
  - Description of processing areas
  - Activities in adjacent areas
  - Product, personnel, equipment and waste flows
- Specific Systems
  - Water, HVAC, facility controls, computer systems
- Contamination/Cross-Contamination Issues
  - Equipment cleaning, air handling, decontamination

Guidance on Applicable Regulations

- Describes applicable provisions in the HCT/P regulations, CGMPs, biologics regulations in 21 CFR Parts 600 - 680
  - Formatted to follow CGMP subparts
- Establishment Registration and Listing
- Current Good Manufacturing Practice (CGMP) and Current Good Tissue Practice (CGTP)
- Label and Labeling content
- Holding and Distribution
- Laboratory Controls
- Records and Reports
- Failure investigations, tracking, complaints, returned and salvaged HPC-C

Postmarketing Activities

- Clinical Outcome Data Collection
  - Recommend analysis of clinical data from transplant centers as quality indicator
  - Should evaluate data to determine whether AEs or other unexpected outcomes may be due to manufacturing problems
- Changes to be Reported (21 CFR 601.12)
- Adverse Experience Reporting (21 CFR 600.80)
- Biologic Product Deviation Reporting (21 CFR 600.14(d))

Next steps

- Review and address comments
- ? Public meeting
- Finalize Guidance
  - Intend to include date for implementation of IND/BLA requirement (ending period of IND enforcement discretion)
- License applications accepted at any time

Device Final Rule and Special Control Guidance

- Rule classifies cord blood processing system and container into class II (special controls) - published 1/31/07
- Guidance for Industry: Class II Special Controls Guidance Document - Cord Blood Processing Systems and Storage Containers
  - Describes means by which the cord blood processing system and container may comply with the requirement of special controls for class II devices
  - Immediately in effect but subject to comment in accordance with the agency's good guidance practices

Guidance: HCT/Ps Tested Using Pooled Specimens or Diagnostic Tests

- Published 1/23/07; for immediate implementation
- Comments to the docket accepted
- For HCT/Ps recovered after 5/25/06 to 30 days after publication
- Addresses:
  - Distributed HCT/Ps and those in inventory
  - Need for HCT/P deviation reports if distributed
  - Retesting/labeling for future distribution of HCT/Ps in inventory

Testing Guidance – cont.

- FDA is exercising enforcement discretion to allow distribution of these HCT/P
- Limited to the two testing deficiencies
- Pertains to recently regulated living donor HCT/P (hematopoietic stem/progenitor cells and reproductive cells and tissues)
- For distributed HCT/Ps, deviation reports only required for hematopoietic stem cells from first or second degree blood relatives
  - One report for all affected HCT/Ps

Testing Guidance: HCT/P Retesting Before Distribution

- Recommend using original donor sample
  - Tested in accordance with the manufacturer's instructions and found negative/nonreactive
  - New specimen OK
- If retesting not feasible
  - Documentation recommended in files
  - Physician notification
  - Labeled "WARNING: Advise patient of communicable disease risks"

Testing Guidance: Retesting Donors

- If you cannot retest the donor, you can distribute these in-inventory HCT/P:
  - Hematopoietic stem/progenitor cells (other than autologous)
  - Cryopreserved embryos formed using 3rd party gametes
- If you cannot retest the donor, you cannot distribute cryopreserved semen or oocytes from anonymous or directed donors